REMARKS

Claims 24-43 were previously pending. Applicants have canceled claims 25, 31-32 and 43 without prejudice to, or disclaimer of, the subject matter contained therein. Applicants maintain that the cancellation of a claim makes no admission as to its patentability and reserve the right to pursue the subject matter of the cancelled claim in this or any other patent application. Applicants have amended claims 24, 26-29, and 34, and added new claims 44-45. Support for these amendments can be found throughout the specification as filed, for example, at page 11, lines 9-10; page 95, lines 5-8; page 98, lines 24-25; page 101, line 24-27; page 102, line 10 through page 104, line 12; and, original claim 2. Applicants submit that no new matter is added and request entry of the amendments. Claims 24, 26-30 and 33-42 and 44-45 are pending.

35 U.S.C. § 102(b) and (e)

Claims 24-37 and 39-43 are rejected under 35 U.S.C. § 102 as anticipated by Bennett et al. (US 6,077,833). The Office asserts that Bennett '833 teaches an antisense oligonucleotide of SEQ ID NO: 22 which targets and inhibits expression of ICAM-1 of SEQ ID NO: 138 in humans, which optionally comprises the recited modifications, and which reduces eosinophilia in a human, and which antisense is optionally co-administered with a steroidal anti-inflammatory agent. *Office Action* at page 2-3. Applicants respectfully traverse. Applicants are not aware of any portion of Bennett '833 which supports this assertion, and respectfully requests that the Office clarify where support for this statement is found in the cited references. However, in order to further prosecution, Applicants have amended the claims.

Currently pending independent claim 24 recites a method of reducing eosinophil recruitment into the lung of a human by administering the compound into the lung. Applicants are not aware of any portion of Bennett '833 which discloses the administration of an oligonucleotide compound targeting ICAM-1 into the lung of a human as recited in claim 24. As the cited reference does not expressly or inherently teach every limitation of claim 24 and the claims that depend therefrom, Applicants request that the rejection of claims as anticipated by Bennett '833 be withdrawn.

35 U.S.C. § 103(a)

Claims 24-43 are rejected under 35 U.S.C. § 103(a) as obvious over Bennett et al. (WO 92/03139) and Bennett et al. (US 6.077,833) in view of Cook et al. (US 6,440,943) and Wollyniec et al. (Am. J. Resp. Cell & Molec. Biol., 18:777-785 (1998)), further in view of Wang et al. (US 6,403,566). The Office asserts that Bennett '139 discloses the antisense of SEQ ID NO: 22, including modifications; that Bennett '833 discloses antisense of SEQ ID NO: 22 and modifications, "which antisense inhibits the expression of ICAM 1, and reduces eosinophilia in a human," and which is optionally administered with a steroidal anti-inflammatory agent; Cook is cited for disclosing the design, synthesis and use of oligonucleotides targeting ICAM-1, and "therapeutic approaches to treating inflammatory diseases and disorders using these antisense, as well as teaching in vitro assays for eosinophil infiltration;" Wollyniec is cited for teaching reduced inflammation and eosinophilia in ICAM-1 deficient mice; and, Wang is cited for disclosure of bicyclic sugar modifications. *See Office Action* at pages 3-5.

The Office argues that it would be obvious to utilize the antisense oligonucleotide of SEQ ID NO: 22 to target ICAM-1, and to inhibit ICAM-1 to treat eosinophilia because "ICAM-1's involvement in inflammation and eosinophilia was well known in the art, as taught previously by Bennett, Bennett, Cook and Wollyniec." *Id.* at page 6. The Office concludes that one of skill in the art "would have reasonably expected that SEQ ID NO. 22, and including the modifications claimed, would provide for inhibition of ICAM1 expression in vitro and in vivo, and would provide for the treatment effects claimed, including reducing inflammation and reducing eosinophilia, relying on the prior art teachings of Bennett, Bennett, Cook, Wang and Wollyniec." *Id.* Applicants respectfully traverse.

To establish a *prima facie* case of obviousness, the Office must establish that there is a reasonable expectation of success in practicing the claimed invention. In the instant case, there must be a reasonable expectation of success in being able to administer the claimed compounds via the lung such that ICAM-1 expression is inhibited and eosinophil recruitment into the lung is reduced.

Applicants are not aware of the disclosure in either of the Bennett et al. references, Wang et. al., Cook et al. or Wolyneic et al. regarding the administration of any oligonucleotide compounds into the lung, including oligonucleotide compounds directed to ICAM-1 specifically.

Thus, none of the cited references provide a reasonable expectation that oligonucleotide compounds generally, or ICAM-1 compounds specifically, can be successfully administered via the lung.

In addition, none of the cited references disclose that oligonucleotide compounds targeting ICAM-1 reduce eosinophil recruitment into the lung regardless of the route of administration, and particularly when administered via the lung.

The Office asserts that Bennett '833 discloses antisense of SEQ ID NO: 22, "which antisense inhibits the expression of ICAM 1, and reduces eosinophilia in a human." *Office Action* at 5. Applicants are not aware of any portion of Bennett '833 which supports this assertion, and respectfully requests that the Office clarify where support for this statement is found in the cited references. In fact, Applicants are not aware of the mention of eosinophils or eosinophilia anywhere in either of the Bennett et al. references, or in the Wang et al. reference.

The only disclosure regarding eosinophils and ICAM-1 in Cook is the following single sentence: "Moreover, intraperitoneal administration of a monoclonal antibody to ICAM-1 decreases ovalbumin-induced eosinophil infiltration into skin in mice (Hakugawa et al., J. Dermatol., 1997, 24, 73)." *Cook* at col. 30, line 33-36 (emphasis added). There are numerous differences between the claimed method and the disclosure in Cook which makes this disclosure irrelevant to providing a reasonable expectation of successfully practicing the claimed methods: the disclosure relates to ICAM-1 antibodies, not oligonucleotide compounds; the disclosure relates to i.p. administration of the antibodies, not administration into the lung; and the result relates to eosinophil infiltration into the skin, not the lung. Thus Cook does not provide a basis for concluding there is a reasonable expectation of success in practicing the claimed methods.

The Office asserts that Wolyniec "teach reduced inflammation and eosinophilia in ICAM-1 deficient mice." *Office Action* at page 5 (citations omitted). According to the reference, ICAM-1 knockout mice were tested in an animal model of asthma. While the ICAM-1 knockout mice had reduced eosinophilia in the lung compared to wild type mice, the authors urge caution in drawing conclusions based on the experiments:

> [L]imitations in forming conclusions from gene-knockout mice should be considered. As an example, Kumasaka and colleagues have described a role for ICAM-1 in a model of endotoxin-induced lung neutrophilia. Antisense oligonucleotides and monoclonal antibodies to ICAM-1 provided inhibition of the lung neutrophilia, whereas the ICAM-1 gene knockout was comparable to the

> wild type. *Wolyniec* at page 778, left col., first full paragraph (emphasis added, citation omitted).

It is clear from this paragraph that antisense, antibody, and gene knockout experimental results for ICAM-1 are not necessarily predictive of each other. Thus, the ICAM-1 antibody and gene knockout evidence in Cook and Wolyniec does not provide a reasonable basis to believe that oligonucleotide compounds targeting ICAM-1 administered via the lung will also reduce eosinophilia.

This assertion is supported by an additional example where the successful inhibition of a target *in vivo* by a non-oligonucleotide compound was not predictive of the *in vivo* activity of oligonucleotide compounds to the same target, even where the oligonucleotide compounds worked *in vitro*. Appellants submit herewith evidence regarding the MAP kinase JNK, which is known to be involved in pulmonary inflammation and eosinophilia.

Wong (*Curr. Opin. Pharmacol.*, 2005, **5**:264-271; submitted herewith as Exhibit 1) discloses that a non-oligonucleotide specific inhibitor of JNK reduces eosinophilia in the lung of rat and mouse models of pulmonary inflammation. *Wong* at page 269, col. 1 and Table 1. This is similar to the disclosure in the cited references relied on by the Office in the instant case – non-oligonucleotide compounds targeting ICAM-1 (e.g., antibodies and gene knock-outs) are effective *in vivo* in reducing eosinophilia in skin and lung. Therefore, according to the Office's reasoning in the instant case, because non-oligonucleotide inhibitors of JNK reduce eosinophilia *in vivo* as disclosed in Wong, antisense to JNK that are active *in vitro* would be expected to reduce eosinophilia *in vivo* as well. However, this conclusion is not supported by the evidence.

Appellants submit herewith as Exhibit 2 a declaration by Brett P. Monia, an expert in the field with extensive knowledge of oligonucleotide compounds. The declaration discloses that two antisense molecules to JNK, selected on the basis of their *in vitro* inhibitory activity, were ineffective in preventing airway hyperresponsiveness or eosinophil recruitment into the lungs in a mouse model of airway hyperresponsiveness at three different doses. The mouse model used in these studies is very similar to the model used in Examples 30-32 of the instant application, and the JNK antisense were administered into the lung as presently recited in the instant claims. Thus, in spite of the successful inhibition of eosinophilia using a non-oligonucleotide inhibitor of

JNK as disclosed in Wong, antisense to JNK that were active *in vitro* were not effective at preventing eosinophil recruitment when administered via the lung.

These results further support the cautionary note made in the Wolyniec reference – antisense, antibody, gene knockout and small molecule inhibitor studies are not interchangeable. The knowledge that a particular target is involved in eosinophilia, and that inhibiting the target using non-oligonucleotide means reduces eosinophilia, is not sufficient to conclude that oligonucleotide compounds to the same target administered via the lung will have the same effect. Given this evidence, Applicants submit that one of skill in the art would not have a reasonable likelihood of success at practicing the claimed methods based on the references cited by the Office in the instant case.

In view of the lack of a reasonable expectation of success, Applicants respectfully submit that the Office has failed to establish a *prima facie* case of obviousness. For at least this reason, Applicants respectfully request reconsideration and withdrawal of the rejection of the claims under 35 U.S.C. § 103(a) as obvious over the cited references.

No Disclaimers or Disavowals

Although the present communication may include alterations to the application or claims, or characterizations of claim scope or referenced art, Applicants are not conceding in this application that previously pending claims are not patentable over the cited references. Rather, any alterations or characterizations are being made to facilitate expeditious prosecution of this application. Applicants reserve the right to pursue at a later date any previously pending or other broader or narrower claims that capture any subject matter supported by the present disclosure, including subject matter found to be specifically disclaimed herein or by any prior prosecution. Accordingly, reviewers of this or any parent, child or related prosecution history shall not reasonably infer that Applicants have made any disclaimers or disavowals of any subject matter supported by the present application.

CONCLUSION

Applicants submit that the present application is in condition for allowance and respectfully requests an action to that effect. If any issues remain, the Examiner is invited to

contact Applicants' counsel at the number provided below in order to resolve such issues promptly. Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

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